



COUPLING SYRINGE SYSTEM AND METHODS FOR OBTAINING A MIXED COMPOSITION

Related Applications

- 5 This application is a continuation-in-part of U.S. Patent Application Serial No. 09/405,463, filed September 25, 1999, which application is incorporated herein by reference.

Background of the Invention

- 10 A large number of drugs and other medicaments are routinely prepared and administered to patients in a health care facility. Sometimes, two components of a therapeutic composition are required to be mixed immediately prior to administration. One method for mixing therapeutic compositions immediately prior to administration includes mixing two solutions in a mixing vessel,
15 whereupon the mixture is drawn into a syringe, and the resulting mixed composition is then applied to an appropriate site of the patient. However, this process is often cumbersome, a significant amount of the drug may be lost, and the time between the mixing and the application is often too long with sensitive compositions (i.e., compositions that, upon mixing, must be immediately
20 administered).

- Another method for mixing therapeutic compositions immediately prior to administration employs two syringes that are clamped together. Output ends of the syringes are inserted into a Y-shaped coupling device having two input openings and a single output opening. Mixing occurs in the Y-shaped coupling
25 device or in a needle connected to the single output end of the Y-shaped coupling device. However, with this type of arrangement, control over the degree of mixing does not exist and the degree of mixing, therefore, may be inadequate.

 Another method for mixing therapeutic compositions immediately prior to

administration includes coupling two syringes with an independent coupling means, thereby allowing the contents of one syringe to be mixed with the contents of the other coupled syringe. The independent coupling means, however, provides a space where there is very little agitation due to plug flow of the contents. The contents, therefore, do not mix well. Additionally, when the syringes are uncoupled (i.e., disengaged), the contents have to be aspirated out of the independent coupling means or they will be lost. In addition, the independent coupling means must be removed and discarded before attaching a needle to the delivery or injection syringe.

U.S. Patent No. 4,994,029 (the '029 patent) discloses a syringe mixer and injector device formed of an injector and an adapter having opposed interconnectable nozzles on their facing ends and sockets and a short tubular spike in each socket to penetrate the stopper of a vial when connected to that socket. *See*, the '029 patent col. 2, ll. 24-31. It is among the additional objects of the invention to provide such a device which can be used with a receiving vial charged with a medicament solid or liquid, and a charging vial charged with a medicament liquid for one-way transfer to the receiving vial for admixing the medicaments therein without retransfer to the charging vial. *Id.* at col. 2, ll. 38-24 and col. 6, ll. 23-30. The injector inner end has a connection, provided with a nozzle recess containing a tapered, e.g. central, spout defining the inner terminus of pathway 5 and a lock connection formation, such as a luer lock tab, arranged to form a male connection formation for interconnecting releasably with mating parts on adapter 30. Col. 4, ll. 5-12. Since the '029 patent explicitly discloses that the system is made for one-way transfer, without recharging the charging vial, it would not be suitable for the recombination of materials between two syringes.

Since the system disclosed in the '029 patent was not contemplated for multiple-pass use (i.e., recombination of materials between two syringes), the skilled artisan would not use the '029 patent disclosure for a syringe system

wherein multiple-pass use is desired. This is so because a system not contemplated for multiple-pass use, that is nonetheless employed for multiple-pass use, can result in an appreciable amount of sample loss (e.g., leakage). This is especially troublesome when the drug is expensive (e.g. leuprolide acetate).

- 5 This is also troublesome since the U.S. Food and Drug Administration (FDA) requires that the health care professionals administer an active ingredient in a precise and known amount. Obviously, this requirement cannot be met when there is an appreciable amount of sample loss due to the syringe assembly.

- 10 U.S. Patent No. 6,223,786 (the '786 patent) is directed to devices and methods for mixing medication and filling an ampule of a needle-less injector prior to an injection, which includes a reagent holder and a diluent holder. *See*, the '786 patent, col. 2, ll. 6-15. The diluent holder includes a plunger which is depressed to load the diluent from the diluent holder into the reagent holder to mix with the reagent to produce a liquid medication for filling the ampule of the
- 15 needle-less injector. *Id.* at col. 2, ll. 20-25. In further embodiments, the reagent holder further includes a reagent plunger rod. *Id.* at col. 2, ll. 24-26. There is no disclosure or suggestion either explicitly or implicitly to include a male or female end forming a fluid tight engagement. In fact, the only engagement disclosed is a thread like engagement without any mention to fluid tightness. Moreover, the
- 20 engagement disclosed by the '786 cannot be locked, as the threaded engagement has no means of locking.

- In the most simplistic embodiment, the '786 patent discloses a four part system: diluent holder, support brushing, reagent holder, and the needleless injector; while the '029 patent discloses a four part system: injector, plunger vial, adaptor and charging vial. The presence of multiple (e.g., four) components
- 25 increases the likelihood of human error when mixing and administering a drug. Additionally, the presence of multiple components increases the likelihood of an occurrence of sample loss (e.g., leakage).

Thus, there is a need for a syringe system wherein components of a composition can be easily mixed by the end user without losing a significant amount of mixed composition during the mixing process and wherein the mixed composition can be easily and rapidly administered to a patient. Such a syringe system will have a relatively few number of interconnecting parts, to minimize human error and to minimize sample loss. Additionally, the syringe system will effectively mix the contents located therein without sample loss, such that it will be approved by the FDA when used with drugs that must be administered in a known, discrete and precise amount (e.g., leuprolide acetate).

Summary of the Invention

The present invention provides a syringe system wherein components of a composition can be easily mixed by the end user without losing a significant amount of mixed composition during the mixing process and wherein the mixed composition can be easily and rapidly administered to a patient. The syringe system has a relatively few number of interconnecting parts, to minimize human error and to minimize sample loss. Additionally, the syringe system effectively mixes the contents located therein without sample loss, such that it can be approved by the FDA when used with drugs that must be administered in a known, discrete and precise amount (e.g., leuprolide acetate).

The present invention provides a coupling syringe system for obtaining a mixed composition, a method for forming a mixed composition that employs such a coupling syringe system, and a method for administering a mixed composition to a patient, that employs such a coupling syringe system.

The coupling syringe system includes a first syringe, a first syringe plunger, a second syringe, and a second syringe plunger. The first syringe includes a first syringe barrel having a first syringe open proximal end and a first syringe distal end. The first syringe further includes a first syringe tip with a male end portion,

wherein the male end portion has a locking ring and a tip. The first syringe barrel has a first syringe inner surface. The first syringe plunger is slidably disposed within the first syringe barrel. The first syringe plunger is in fluid-tight engagement with the first syringe inner surface. The second syringe includes a
5 second syringe barrel having a second syringe open proximal end and a second syringe distal end. The second syringe further includes a second syringe tip with a female end portion, wherein the female end portion includes one or more exteriorly protruding members adapted to detachably fit the locking ring. The second syringe barrel has a second syringe inner surface. The second syringe
10 plunger is slidably disposed within the second syringe barrel. The second syringe plunger is in fluid-tight engagement with the second syringe inner surface. The female end portion has an opening therein. The opening is sized and configured to receive the tip of the male end portion therein. The locking ring couples the first syringe to the second syringe when the tip of the male end portion is disposed
15 within the female end portion, forming a fluid tight engagement.

Brief Description of the Drawings

FIG. 1 illustrates a coupled syringe system with a mixed composition formed from introducing the composition of the syringe with the male end portion into the
20 syringe with the female end portion.

FIG. 2 illustrates a coupled syringe system with a mixed composition formed from introducing the composition of the syringe with the female end portion into the syringe with the male end portion.
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FIG. 3 illustrates a syringe with a female end portion.

FIG. 4 illustrates a syringe with a male end portion.

FIG. 5 illustrates a coupled syringe system with a mixed composition formed from introducing the composition of the syringe with the female end portion into the syringe with the male end portion.
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disposed on the female end portion of the second syringe 14 as shown in Fig. 3. The locking ring 11 is designed to interlock the first syringe 13 (i.e., the syringe including the male end portion) and the second syringe 14 (i.e., the syringe including the female end portion). In addition, the locking ring 11 is configured to detachably connect to a discharge assembly 15. Specifically, the discharge assembly 15 can include a needle 16 (see Fig. 6).

As shown in Figs. 1, 2, and 5, syringe system 1 also includes a second syringe 14 having a barrel 18. The barrel 18 has a distal end 19, an open proximal end 20, and a generally cylindrical wall 21 extending between the ends to define a fluid receiving chamber 22. Cylindrical wall 21 of the second syringe barrel defines an outside diameter along much of its length. An outwardly projecting finger flange 23 is defined near proximal end 20 of the second syringe barrel 18 for facilitating digital manipulation of the second syringe 14. As shown in Fig. 3, distal end 19 of the second syringe barrel is characterized with a tip 25. Tip 25 is provided with a fluid passage 26 extending therethrough and communicating with fluid receiving chamber 22. The tip 25 is also provided with a female end portion 27 wherein the female end portion 27 is configured to detachably connect to the locking ring 11. The female end portion 27 includes one or more (e.g., 1, 2, 3, or 4) exteriorly protruding members 30 adapted to detachably engage the locking ring 11. The protruding members 30 are configured such that they can thread into the locking ring 11.

As shown in Figs. 1, 2, 4, and 6, a plunger 40 is disposed in fluid receiving chamber 6 and is in sliding fluid-tight engagement with cylindrical wall 5 of syringe barrel 2. Sliding movement of plunger 40 in a distal direction causes the composition (i.e., solid, liquid, or mixture thereof) in chamber 6 to be expelled through passage 9 of tip 8 (see Fig. 4) and into fluid receiving chamber 22 (see Figs. 1, 2, 3, and 6) thereby mixing the composition (i.e., solid, liquid, or mixture thereof) of chamber 6 with the composition (i.e., solid, liquid, or mixture thereof)

of chamber 22. Conversely, sliding movement of plunger 40 in a proximal direction draws the composition (i.e., solid, liquid, or mixture thereof) in chamber 22 through passage 26 and into fluid receiving chamber 6 thereby mixing the composition (i.e., solid, liquid, or mixture thereof) of chamber 26 with the
 5 composition (i.e., solid, liquid, or mixture thereof) of chamber 22. It is appreciated that those skilled in the art understand that any combination of the above steps can be carried out and repeated until such time as an effective amount of mixing is attained.

As shown in Figs. 1, 2, 3, and 6, a plunger 90 is disposed in fluid receiving
 10 chamber 22 and is in sliding fluid-tight engagement with cylindrical wall 21 of syringe barrel 18. Sliding movement of plunger 19 in a distal direction causes the composition (i.e., solid, liquid, or mixture thereof) in chamber 22 to be expelled through passage 26 of tip 25 and into fluid receiving chamber 6 (see Figs. 1, 2, 4, and 6) thereby mixing the composition (i.e., solid, liquid, or mixture thereof) of
 15 chamber 22 with the composition (i.e., solid, liquid, or mixture thereof) of chamber 6. Conversely, sliding movement of plunger 90 in a proximal direction draws the composition (i.e., solid, liquid, or mixture thereof) in chamber 6 through passage 9 and into fluid receiving chamber 22 thereby mixing the composition (i.e., solid, liquid, or mixture thereof) of chamber 6 with the composition (i.e.,
 20 solid, liquid, or mixture thereof) of chamber 22. It is appreciated that those skilled in the art understand that any combination of the above steps can be carried out and repeated until such time as an effective amount of mixing is attained.

As shown in Fig. 6, a discharge assembly 15 can be connected to the locking
 ring 11 of the first syringe 13. More particularly, the discharge assembly 15
 25 includes needle cannula 50 having a proximal end 51, a sharp distal end 52 and a lumen 55 extending therebetween. A hub 75 joined to the cannula so that the lumen 55 is in fluid communication with the hub 75. Tip 8 fits into hub 75 and frictionally engages the hub 75 so that the lumen 55 of needle cannula

communicates with passage through tip 8 and further communicates with fluid receiving chamber 6 of syringe barrel 2. In this embodiment, needle assembly 77 is removably mounted to tip 8. However, it is within the purview of the present invention to include a needle cannula that is directly and permanently mounted to the syringe tip.

As shown in Fig. 6, a needle cover 60 can be removably mounted over needle cannula 50 to prevent accidental sticks prior to use of syringe assembly 70. Needle cover 60 can be removed from syringe assembly 70 immediately prior to use.

In an alternative embodiment, a first securing device can conveniently be mounted on the interior surface of barrel 2 or on the inside of barrel 18. The first securing device, upon engaging with a second securing device mounted on the external surface of plunger 40 or plunger 90, respectively, can prohibit the plunger 40 or the plunger 90 from disengaging from barrel 2 or the barrel 18, respectively.

The first syringe and the second syringe can conveniently be manufactured from any suitable material. Typically, both the first syringe and the second syringe are each independently manufactured from glass or plastic (e.g., polypropylene, polyethylene, polycarbonate, polystyrene, and the like).

The size of both the first syringe and second syringe can independently be any suitable size. Suitable sizes include a syringe barrel of about 0.01 to about 100 cc, about 0.1 cc to about 50 cc, about 0.1 cc to about 25 cc, or about 0.5 cc to about 10 cc.

The first syringe 13 (i.e., the syringe including the male end portion and locking ring) can conveniently be manufactured by any suitable process. The first syringe can conveniently be manufactured by an injecting molding process where the entire syringe is made as one unit. Alternatively, the first syringe can be manufactured by independently molding the syringe and locking ring and then mounting (i.e., attaching) the locking ring and first syringe. Preferably, the locking ring is permanently attached to the first syringe. Although the ring can also be

mounted coaxially and rotably with tip 8 by a flange and seal configuration. In this configuration, the ring can be rotated around the tip. Typically, the locking ring is permanently attached to the first syringe by welding the two pieces together.

5 The second syringe 14 (i.e., the syringe including the female end portion) can conveniently be manufactured by any suitable process. The second syringe can be manufactured by an injecting molding process where the entire syringe is made as one unit.

Each composition to be combined with a syringe can independently be a solid, liquid, or mixture thereof. In addition, the solid can be a powder or crystalline
10 material. As used herein, a mixture of a solid and a liquid can be a heterogeneous phase (e.g., an emulsion or a colloidal suspension). Alternatively, a mixture of a solid and a liquid can be a homogeneous phase (i.e., a solid completely dissolved in a liquid).

Each composition can independently include one or more (e.g., 1, 2, or 3)
15 compounds. In addition, the compound of the composition can be a drug delivery system, a drug (i.e., pharmaceutical) or a pharmaceutically acceptable salt thereof, a liquid carrier, a liquid, a lipid formulation, or a vaccine.

Any suitable drug delivery system can be employed. A suitable drug delivery system includes, but is not limited to, is the Atrigel ® delivery system mixed with
20 doxycycline or leuprolide acetate. The Atrigel ® system is described in U.S. Patent No. 5,278,201, the disclosure of which is incorporated herein by reference.

Any suitable drug (i.e., pharmaceutical) or pharmaceutically acceptable salt thereof can be employed. Suitable classes of drugs include antibiotics, peptides, hormones, analgesics, growth factors, and any agent described in US. Patent No.
25 B14938763, the disclosure of which is incorporated herein by reference. The drug can exist as a solid (e.g., crystal or powder), an oil, or as a liquid. In addition, the drug may exist in a microcapsule containing the drug or as a microparticle.

Any suitable liquid carrier can be employed. Suitable liquid carriers include a

collagen solution, a sterile aqueous solution, a sterile saline solution, an alcoholic solution, or any suitable mixture thereof. In addition, the liquid carrier can be an emulsion formed from a mixture of an oil or lipid with a sterile aqueous solution or a sterile saline solution.

5 Specifically, the liquid drug delivery system can be the Atrigel ® system mixed with a powder drug (e.g., doxycycline or leuprolide acetate).

Specifically, the drug can be an antibiotic or growth factor.

Specifically, the liquid carrier can be a collagen solution and a powder drug.

10 Specifically, the liquid carrier can be a sterile aqueous or a sterile saline solution and a powder drug.

Specifically, the liquid can be an alcohol and a drug mixed with a sterile saline or a sterile aqueous solution.

Specifically, the lipid formulation can be mixed with a sterile aqueous solution or a sterile saline solution to form an emulsion.

15 Specifically, the liquid carrier (e.g., a sterile aqueous solution or a sterile saline solution) can be mixed with a microcapsule or a microparticle containing drug.

Specifically, the vaccine solution can be mixed with an oil to form an emulsion.

20 Any suitable method of administration can be employed. Typically, the mixed composition can be administered to a patient by intravenous, intramuscular, intraperitoneal, or subcutaneous routes.

Examples

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Both the amount of drug and the drug content, delivered from a syringe system of the present invention, is relatively uniform. Additionally, there is relatively low sample loss when delivering a drug from syringe system of the present invention.

Example 1.

The LA-2575 30.0 mg drug product when injected subcutaneously forms a
5 biodegradable implant that delivers 30.0 mg of leuprolide acetate (LA) over a four-
month period. The drug product is composed of two separate syringes. Syringe A
with a female Luer Lok fitting contains the drug delivery vehicle, and Syringe B
with a male Luer Lok fitting contains lyophilized LA. To constitute the product for
injection, Syringe A and Syringe B are connected, and the contents are passed back
10 and forth until blended. After mixing, the two syringes are separated, a
hypodermic needle is attached to Syringe B, and the constituted drug product is
administered subcutaneously to the patient.

A fraction of the constituted drug product is trapped in the hub of Syringe A after
the mixing process and in the hub and needle of Syringe B after injection. To meet
15 the targeted delivery values, this retained drug product must be accounted for
when calculating the fill weights for both syringes. Also, the amount of material
and drug delivered from the mixed syringe must be consistent in quantity to meet
strict FDA rules for administered drug. To determine whether the amount of
material and drug administered was consistent, an experiment was performed with
20 the following supplies:

Syringe A, a 1.2 ml syringe (UltraTek) molded with a female Luer-
Lok[®] fitting, contains the vehicle 75:25 Poly (D,L-lactide-co-glycolide)
(PLG) dissolved in a biocompatible solvent N-methyl 2-pyrrolidone
(NMP). The fill weight was 560 mg vehicle.

25 Syringe B, a 1.0 mL syringe (Becton-Dickinson) molded with a male Luer-
Lok[®] fitting, contains lyophilized LA. The fill weight was 35.8 mg of
lyophilized LA.

Each of three lab analysts constituted 10 replicate units using 30 mixing cycles and determined delivered mass and %LA content. The data given in the table show that the delivered mass was consistent with a delivered mass of 504.4 ± 6.55 mg and the mixing was uniform with a drug content of 5.6 ± 0.19 %. These data show that

5 the syringe coupling system gives uniform mixing of the contents and reproducible delivery of the mixed mass.

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Analyst	Sample	30 Cycles	
		Del. Mass	LA
		(mg)	(%)
1 (ST)	1	508.6	5.7%
	2	517.3	5.7%
	3	512.8	5.8%
	4	514.9	5.7%
	5	508.7	5.7%
	6	505.9	5.5%
	7	504.4	5.8%
	8	506.2	5.7%
	9	512.6	5.8%
	10	503.6	5.7%
2 (SV)	1	508.8	5.7%
	2	504.2	5.7%
	3	511.7	5.6%
	4	509.9	5.6%
	5	501.0	5.7%
	6	502.3	5.5%
	7	500.1	5.6%
	8	499.7	5.7%
	9	505.1	5.7%
	10	505.0	5.7%
3 (RM)	1	494.9	5.1%
	2	499.4	5.4%
	3	501.6	5.7%
	4	506.0	5.7%
	5	497.9	5.6%
	6	505.3	5.7%
	7	501.0	5.4%
	8	502.8	5.0%
	9	485.8	5.2%
	10	494.5	5.6%
Mean		504.4	5.6%
SD		6.55	0.19%
% RSD		1.3%	3.5%

Example 2.

The 6-Month ELIGARD 45.0 mg drug product when injected subcutaneously forms a biodegradable implant that delivers 45.0 mg of leuprolide acetate (LA) over a six-month period. The drug product is composed of two separate syringes.

- 5 Syringe A with a female Luer Lok fitting contains the drug delivery vehicle, and Syringe B with a male Luer Lok fitting contains lyophilized LA. To constitute the product for injection, Syringe A and Syringe B are connected, and the contents are passed back and forth until blended. After mixing, the two syringes are separated, a hypodermic needle is attached to Syringe B, and the constituted drug product is
- 10 administered subcutaneously to the patient.

- A fraction of the constituted drug product is trapped in the hub of Syringe A after the mixing process and in the hub and needle of Syringe B after injection. To meet the targeted delivery values, this retained drug product must be accounted for when calculating the fill weights for both syringes. An experiment was conducted
- 15 to determine the amount of total mass delivered, the amount of drug, and the drug content when the two syringes were mixed. The following supplies were used in this experiment:

- Syringe A, a 1.2 ml syringe (UltraTek) molded with a female Luer-Lok® fitting, contains the vehicle 85:15 Poly (D,L-lactide-co-glycolide) (PLG) dissolved in a biocompatible solvent N-methyl 2-pyrrolidone (NMP). The fill weight of the polymer vehicle was 410 ± 2 mg.
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Syringe B, a 3.0 mL syringe (Becton-Dickinson) molded with a male Luer-Lok® fitting, contains lyophilized LA. The fill weight of this syringe was 56.3 mg of LA.

- 25 Each of three lab analysts constituted six replicate units using 60 mixing cycles and determined delivered mass and %LA content. The results given in the table

show that the delivered mass was consistent with 371.4 ± 4.5 mg, the amount of drug delivered at 45.5 ± 0.8 mg, and the drug content at $12.3 \pm 0.2\%$. These data show that the unique syringe coupling system gives both uniform mixing of the contents and reproducible delivery of the mixed mass.

Analyst	Sample	60 Cycles		
		Del. Mass	LA Rev	LA Recov
		(mg)	(mg)	(%)
1 (ST)	1	376.8	46.0	12.2%
	2	376.0	46.3	12.3%
	3	360.8	43.6	12.1%
	4	373.2	45.7	12.2%
	5	378.3	46.2	12.2%
	6	372.8	46.9	12.6%
2 (SK)	1	376.6	45.2	12.0%
	2	372.4	45.4	12.2%
	3	365.1	44.7	12.2%
	4	368.1	45.5	12.4%
	5	373.5	45.8	12.3%
	6	372.9	46.5	12.5%
3 (MA)	1	372.1	44.4	11.9%
	2	370.4	44.7	12.1%
	3	366.5	45.4	12.4%
	4	367.1	45.5	12.4%
	5	371.1	45.9	12.4%
	6	370.6	45.4	12.3%
Mean		371.4	45.5	12.3%
Std. Dev		4.5	0.8	0.2%
% RSD		1.2%	1.8%	1.3%